The interview among Examiners Andres and Spector and Dr. Michael Tovey, who is one of the present inventors, and the undersigned attorney, conducted on November 3, 2000, is hereby gratefully acknowledged. In this interview, applicant discussed why it would not be obvious to combine Cummins with either Iida or Samo, particularly since both of the secondary references relate only to prevention, and, therefore, there is no motivation to increase the dosage of Cummins. Additional publications were discussed which support the fact that those skilled in the art would not expect references related to prophylaxis would make obvious the treatment of rhinoviral infections. Language which would avoid anticipation in view of such newly cited documents was also discussed. The arguments presented at the interview will be repeated herein.

Claims 15-18 and 24 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

Claims 15-18 and 24 have now been deleted, thus obviating this rejection.

Claims 15-18 and 24 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Claims 15-18 and 24 have now been deleted, thus obviating this rejection.

Claim 9 has been rejected under 35 U.S.C. §103 as being unpatentable over Cummins in view of Iida. The examiner states that Cummins teaches the use of interferon in the treatment of viral infection and that Iida teaches other cytokines having beneficial effects and further teaches intranasal administration. Thus, the examiner considers the combination of two agents known to be beneficial individually to be *prima facie* obvious. This rejection is respectfully traversed.

Claim 9 is allowable for the same reason as claim 1 from which it depends for the reasons which will be discussed below relating to the rejection of record of claim 1 over the same references. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 15-18 have been rejected under 35 U.S.C. §102 as being anticipated by Samo.

This rejection has been obviated by the deletion of claims 15-18.

Claims 1-5 and 7-24 have been rejected under 35 U.S.C. §103 as being unpatentable over Cummins in view of either Samo or Iida. The examiner states that the prior art fairly provides motivation to use doses higher than those exemplified by Cummins but lower than those exemplified by Samo and Iida because all of the prior art dosages were found

to be effective for treatment of viral infection. The examiner states that the artisan would have reasonably expected that any intermediate range would likewise be effective. The examiner states that one skilled in the art would expect that administration of higher doses would result in absorbed levels at least equivalent to those resulting from the doses used by Cummins and, thus, one would expect that higher doses would result in effective treatment of a viral infection. The examiner refused to consider applicant' post-filing date evidence that Cummins teaches away from higher doses. This rejection is respectfully traversed.

Cummins teaches a maximum of about 5 IU/kg/day. Neither Samo nor Iida would suggest to one of ordinary skill in the art the use of larger amounts of interferon using the mode of delivery of Cummins as neither Samo nor Iida relate to the treatment of rhinovirus, or any other condition. Both Samo and Iida are limited to prophylaxis against rhinoviral infection. The title of Samo is "Intranasally Applied Recombinant Leukocyte A Interferon in Normal Volunteers", and the conclusion in the last paragraph is that rIFN has been shown to be efficacious in the <u>prevention</u> of illness after rhinovirus challenge. Similarly, Iida's title relates "protective activity". Figure 2 shows that in the one example, where the interferon was administered one day after

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infection, the results were negligible. See page 230, column 2, where it states:

> Although i.n. administration of 100 U IFN-γ either five days, three days, or one day before the infection, showed potent protective activity (88%, 88% and 83%, respectively), post infection administration (simultaneously with and one day after the infection) had no effect (13%).

Other evidence also exists that treatment of rhinovirus (the common cold) by local administration of interferon intranasally is ineffective. Attached hereto is a copy of Hayden et al, "Intranasal Recombinant Alfa-2b Interferon Treatment of Naturally Occurring Common Colds", Antimicrobial Agents and Chemotherapy 32(2):224-230 (1988). The effect of this treatment is succinctly stated as follows in the last sentence of the abstract:

> Nasal sprays of recombinant alfa-2b interferon were not an effective treatment for natural colds and were associated with toxicity.

Also attached is an editorial from the British Medical Journal: Scott "Interfering with the Real Cold", Br Med J (Clin Res Ed) 292(6533):1413-1414 (1986). Note the first sentence thereof, where it states:

> Intranasal sprays of interferons are effective in volunteers in preventing experimental colds due to rhinoviruses, but they have no appreciable benefit when given after the symptoms have begun.

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Accordingly, those of ordinary skill in the art reading Cummins, Samo and Iida would find no justification in either Samo or Iida for making any modifications whatsoever in Cummins as Cummins relates to the treatment of pathologic conditions, while Samo and Iida relate only to prevention of rhinoviral infections when the interferon is administered prior to infection. Furthermore, other art of record establishes that those of ordinary skill in the art at the time the present invention was made would have understood that administration intranasally to those already having rhinoviral infection is ineffective. Accordingly, no combination of these references teach or make obvious the dosage amounts of the present invention.

Besides the fact that the combination of references does not establish a *prima facie* case of obviousness for the reasons discussed above, there are other reasons why those of ordinary skill in the art would not be motivated to increase the amount of interferon administered by the oromucosal route of Cummins. Those of ordinary skill in the art aware of the state of the art at the time the present invention was made would understand that the mode of treatment in Cummins only works with extremely low doses, and that administration of more provides worse results. As evidence of this, reference is made to U.S. patent 4,820,515 (a copy of which is attached

hereto) to the same inventor (Cummins), who uses the same mode of administration of interferon for antiviral and appetite regulation indications. After discussing the results of his experiments, Cummins '515 concludes at column 12, lines 5-9:

> In summary, human interferon α administered orally at the lowest dose (18.0 IU/lb) appeared to be the most beneficial route and dosage. More interferon appeared not to be better than less interferon.

In a later review by Cummins, previously supplied to the examiner (Cummins et al, J Int Cyt Res, 19:853-857 (1999)), Cummins stated at page 854 in the first paragraph of the conclusions:

> One of the paradoxes of the efficiency in the oral use of IFN is the dose effect. Here, "less" is almost always better than "more." In most of the low dose studies of IFN-α, used orally, where a beneficial dose was identified, increasing the dose did not improve the effect.

While this is a post-filing date publication, it is a review article and many of the publications reviewed are pre-filing date. Note, for example, reference 72 which is Moore et al "Changes in airway inflammatory cell populations in standardbred racehorses after interferon-α administration", Vet Immunol Immunopathol, 49:347-358 (January 1996), a copy of which is attached hereto. Note, for example, Figure 1 at day 8, which shows that the lower doses are significantly better than control, whereas the higher dose is not significantly

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better. Thus, it would not be readily obvious that higher doses of oromucosal administration will provide better results or will even provide comparable results when the inventor of reference D1 urges that low dose is critical.

Higher doses of interferon have been administered parenterally in the prior art for various conditions encompassed by the present claims. However, those of ordinary skill in the art would not consider dosages which are relevant to parenteral administration to be relevant to oromucosal administration as parenteral administration always involves getting interferon into the blood stream, while this does not occur with oromucosal administration.

Reference is made to the comparative experiments in the present specification, particularly Examples 4, 5 and 6. Example 5 clearly shows that while ip and iv administration cause large amounts of biologically active IFN protein to enter the blood stream, no biologically active IFN enters the blood stream following oromucosal dosage. Only fragments of radioactive IFN were found, which would be expected after degradation in the gut. One of ordinary skill in the art would not even expect that such a large protein as IFN would enter the blood stream through the oral mucosa upon oromucosal administration. The protein is simply too large for that. Furthermore, Example 4 shows that cellular proteins known to

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be induced by IFN are not expressed following oromucosal administration of IFN. This supports the conclusion that substantially different mechanisms are at work. Thus, those skilled in the art would not consider dosages effective for parenteral administration to be relevant to dosages effective for oromucosal administration.

As theorized in the present specification at page 2, lines 21-30, the administration of interferon by the oromucosal route does not involve a direct action of exogenously administered IFN, or even the induction of endogenous IFN. Detectable levels of circulatory IFN are not present after oromucosal administration, as discussed above. The inventors now know, and additional results of experimentation to this effect can be provided if the examiner so requests, that migration of immunocompetent cells to the site of tumor cell multiplication is stimulated by this oromucosal contact without direct contact of the interferon on these immunocompetent cells. It can be shown by use of a gene reporter assay that these cells have not come into direct contact with interferon.

In conclusion, oromucosal administration is not considered by one of ordinary skill in the art to be an obvious alternative to parenteral administration when administering large proteins. No one would expect that a

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large protein will pass through the oral mucosa into the blood stream. Indeed, the data in the present specification shows that it does not enter the blood stream. Why then would one of ordinary skill in the art consider using oromucosal administration of such a large protein as interferon for any purpose? The only reference which suggests the use of oromucosal administration of interferon is Cummins, and other Cummins publications disclose that low dose is important and that there is no advantage to using higher doses. Indeed, he suggests that it is worse. In view of the knowledge that proteins as large as IFN would not be expected to pass through the oral mucosa into the blood stream, those skilled in the art would have no reason to believe that larger doses would work with the process of Cummins. On the other hand, the data of the present inventors establishes that the effect of oromucosally administered interferon in accordance with the present invention is indeed dose-dependent. This would not have been obvious to one of ordinary skill in the art at the time the present invention was made in view of the fact that it would not be expected that oromucosal administration of interferon would enter the blood stream (and indeed it does not).

For all of these reasons, those of ordinary skill in the art would have no motivation to substantially increase the

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maximum dosage disclosed by Cummins when administering by the same mode of administration as disclosed by Cummins. Thus, the present claims are not made obvious by any combination with Samo or Iida. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

In order to expedite allowance of this case, applicant wishes to bring to the examiner's attention the Sato and Eby patents, which are of record in this case, but have not been applied in any rejection to date. In order to preempt a possible rejection of the composition claims over one or both of Eby and Sato, the composition claims have now been deleted. Furthermore, in order to preempt a possible rejection of the method claims over Eby or Hayden (1988) as discussed above, applicant proposes to amend claim 1 to insert two provisos. The first is that the oromucosal administration is in a manner which does not involve direct action of the interferon on virally-infected cells. This language is supported by the last paragraph on page 20 of the specification, and particularly in lines 23-24. This will avoid a technical anticipation by the failed experiments of Hayden (1988). The second proviso is that, when the condition is rhinovirus, the interferon is not administered through the mouth by multiple or continuous doses. This proviso is stated in order to avoid a possible new rejection of unamended claim

1 over the Eby patent, which is already of record in this case. Eby specifically states at column 5, lines 43-53:

> This inventor teaches that all ... interferons ... must be administered to the roof of the mouth, the interior cheeks of the mouth, the tongue, the oromucosa, the oropharyngeal mucosa and all other interior surfaces of the mouth and to the throat, about each one to three hours, in a suitable manner and in a sustained way for any common cold treatment to be effective.

This is a clear teaching that sustained administration, each one to three hours, is required in order to be effective. For the present invention, only a single daily dose of administration is necessary (see page 7, line 1, of the present specification). This difference is because Eby believes that his invention is operable because of "absorption" of the interferon (column 1, line 47) into the lymphatic system or otherwise to circulate into the nasal tissue in the locus of infection (column 4, lines 14-15). On the other hand, the present invention does not act by direct action of exogenously administered interferon, as the interferon does not enter the circulatory system. It acts by stimulation of the lymphoid tissues surrounding the nasal, pharyngeal and oral cavities (see the last paragraph on page 20 of the present specification). Note also column 5, lines 27-42, of Eby, which states:

> [T]his inventor now teaches that the reason all ... interferons ... fail or produce

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> limited results is because they are not applied to the lining of the mouth in a sustained and repeated fashion, rather they are applied to the more logical and more obvious treatment locus, the interior of the nose, or by a secondary route such as oral ingestion or by injection.

Thus, Eby specifically teaches that the procedure will fail if administered to the interior of the nose. On the other hand, administering to the interior of the nose is clearly one of the approved means of getting the interferon to the oromucosal cavity in the present invention, as this is what is done in the specific examples. Accordingly, the proviso avoids anticipation by Eby. Furthermore, it would not be obvious to administer interferon to the nose or in a single dose in view of the above-quoted portions of Eby which indicate that administration to the mouth and in a sustained or repeated fashion is critical to effectiveness.

Provisos eliminating disclosed species of a claimed genus to avoid reading on the prior art were held to comply with the written description requirement in *In re Johnson*, 194 USPQ 187, 196 (CCPA 1977).

If applicant had not amended claim 1 and had merely amended claim 15 to insert the subject matter of claim 24, i.e., place claim 24 into independent form, the outstanding rejections would have been overcome. Accordingly, if the examiner wished to reject claim 1 over Eby or Sato, for

example, the examiner would have had to issue a new non-final official action in order to do so. If the examiner had done this, applicant would have had the opportunity to insert the Hayden (1988) reference in an Information Disclosure Statement and to amend the claims at will. As applicant is merely avoiding these two steps by preemptively amending the claims, it is respectfully requested that the examiner enter and consider the amendment, notwithstanding the fact that the application is under final, and it is further requested that the examiner officially cite of record on a form PTO-892 the Hayden 1988 reference, which is merely attached hereto and cited as evidence of unobviousness.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,

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